asserts that the phrase "affecting a biological process" is unclear in how the biological process is affected. Applicants traverse this rejection.

The claims of the invention are to be read in light of the specification. The specification provides ample description of how the peptide compositions of the invention affect biological processes characterized by abnormal cell migration through a physiological barrier such that one of skill in the art would understand the meaning of the phrase "affecting a biological process" in claims 5-7. Among other things and citations, the specification discloses that the peptide of the invention may be used to inhibit PAI-1-dependant cell adhesion, a critical point in cell migration through tissues, and may be used to inhibit several listed disease states associated with undesirable cell migration, including angiogenesis (specification page 14, lines 23-28). One of skill in the art would understand the meaning of claims 5-7 in light of this disclosure and the disclosure of the specification as a whole.

Applicants request that the rejection of claims 5-7 be reconsidered and withdrawn.

Rejection of claims 5-10 and 17-20 pursuant to 35 U.S.C. § 112, first paragraph

Claims 5-10 and 17-20 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification does not enable one of skill in the art to make and use the invention commensurate with the scope of the claims. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for any peptide comprising EEIIMD beyond SGTVASSSTAVIVSARSAPEEIIMD, that affects biological processes such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion, and atherosclerosis. The Examiner concedes that the specification is enabling for EEIIMD and SGTVASSSTAVIVSARSAPEEIIMD for inhibiting PAI-1-dependant adhesion of a cell. The Examiner asserts that a consideration of the Wands factors indicates that one of skill in the art could not practice the invention without undue experimentation. Applicants traverse this rejection.

It is well-settled that applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed

in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

There is no requirement under the current law of enablement that each embodiment be reduced to practice. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991), cited by the Examiner with regard to the written description requirement, made clear that generic claims are not precluded by 35 U.S.C. §112, first paragraph, and that enablement does not require working examples for each species encompassed by a claim. *Accord In re Robbins*, 166 USPQ 552 (CCPA 1970).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

The Examiner cites two references, Ngo et al. (pages 491-495 in The Protein Folding Problem and Tertiary Structure Prediction, Merz and Grand, ed., 1994) and Rudinger (pages 1-7 in Peptide Hormones, Parsons, ed., 1976) as indicative of the state of the prior art and the predictability in the art at the time of filing. Specifically, the Examiner cites these references as examples that "the three dimensional structure of the peptide cannot be based on structure alone." (Office Action of April 10, 2002, page 4, lines 6-7). Applicants respectfully assume that the Examiner meant to assert that the three dimensional structure cannot be based on sequence alone.

Ngo et al. discusses predicting the structure of a compete protein from amino acid sequence alone, and does not address the prediction of the structure of small peptides where experimental evidence exists of the relation of sequence and variants of the sequence to

activity and therefore structure of the peptide. Contrary to Ngo, the specification contains ample disclosure of experimental results and scientific reasoning so that the correlation of structure to sequence is not unpredictable (see, specification page 35 line 8 to page 36, line 27, among other places). Applicants respectfully point out that one or more pages of the Ngo reference appear to be missing from the copy sent with the Office Action, as the text of the first un-numbered page does not logically connect with the text on the second page, page 492. Additionally, at the top of page 492 is apparently the end of the discussion in which the author forms his thesis that computational resources are not sufficient to calculate the structure of a protein from amino acid sequence alone. This omitted discussion presumably includes a teaching of the size of the protein that is the subject of the authors assertions. Applicants request that the entire Ngo reference be sent if the Examiner continues to base this rejection on this reference.

The Examiner cites Rudinger (1975) as indicative of the state of the art at the time of priority filing of the present application, October 17 1997. The Examiner states that the relative skill in the art is high, which is suggestive of a quickly advancing field of technology. A reference that was published 22 years before the filing date of the application cannot be considered indicative of the state of the art at the time of filing in a rapidly advancing field. Futher, the Rudinger reference is inadequate to establish the unpredictability of the art to which the invention pertains as it discusses the ability to predict different aspects of biological activity "a priori" without experimental study (Rudinger page 6, second paragraph) while considerable experimental study is disclosed in the specification.

The Examiner cites webpages by Black (April 27, 1998) and the Mayo Clinic (May 12, 1998) as suggesting complexity in the field of art. However, complexity itself does not result in an invention requiring undue experimentation. On the contrary, both references suggest that the field is predicable enough that treatments of diseases related to abnormal cell migration are in sight. Black characterizes the field of angiogenesis treatment as "extremely hot" (page 1, paragraph 5), and states that four companies are conducting Phase 1 trials for angiogenesis inhibitors, and two are conducting Phase II trials. This degree of success does not suggest a field that is prohibitively unpredictable as researchers are indeed succeeding in developing treatment methodologies. Similarly, the Mayo Clinic reference states that director of the Mayo Clinic program for Phase I testing of new cancer treatments is "optimistic" about

anti-angiogenesis treatments. The issues cited by the Examiner, "appropriate regimens, method of administrations and dosages and who should take them..." (Office Action, page 4, lines 19-20) are all issues that can be resolved by routine experimentation, and do not amount to "undue experimentation."

The specification provides sufficient working examples to indicate that one of skill in the art could make the invention without undo experimentation. There is a working example to show how to determine if a peptide is promoting binding of scuPA to LM-TK- cells (specification, pages 34-39). A "clot lysis" *in vivo* model is described which may be used to determine if a peptide can promote fibrinolysis in mice which have been injected with micro-emboli made from human fibrinogen (specification pages 39-42). Further, other assays to determine the efficacy of treatments on angiogenesis, organogenesis, ovulation, inflammation, cancer and tumor cell invasion and metastasis and atherosclerosis were well known in the art at the time of filing.

Applicants respectfully request that rejection of 5-10 and 17-20 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejection of claims 1, 5-6, 8, 10 and 17 pursuant to 35 U.S.C. § 102(b)

Claims 1, 5-6, 8, 10 and 17 stand rejected under 35 U.S.C. § 102, first paragraph, as being anticipated by Pannekoek. No further identification of the reference is given. Applicants are responding to this rejection with the understanding that the reference cited is International Patent Publication WO 91/05048, in which Pannekoek is the inventor. Applicants traverse this rejection. Applicants respectfully request that the Examiner make the reference of record in the present application in a Form 892.

For a claim to be anticipated by a reference under § 102(b), the reference must disclose every element of the claim. The Examiner cites page 17, lines 31-31 of the Pannekoek reference as teaching the sequence SGTVASSSTAVIVSARSAPEEIIMD. While the Applicants could not find such as sequence at that cite, Applicants concede that such a sequence is taught in the abstract and in claim 1. However, Pannekoek does not teach a peptide with that sequence that reads on the claims 1, 5-6, 8, 10 and 17. Pannekoek refers to the amino acid sequence SGTVASSSTAVIVSARSAPEEIIMD as the sequence in the PAI-1 protein which will be mutated by replacement with another sequence. Pannekoek does not

teach a peptide with the amino acid sequence EEIIMD that has up to 20 amino acid residues on either terminus. Pannekoek does not teach a peptide with the amino acid sequence EEIIMD that has either a hydrogen or amino-terminal blocker group at either terminus. Pannekoek does not teach a peptide with the amino acid sequence EEIIMD that has a hydrogen group at either terminus.

The Examiner asserts that Pannekoek teaches that "the peptide" inhibits thrombin in the presence or absence of vitronectin (Office Action of April 10, 2002, page 8, lines 14-16). However, the Examiner does not cite the passage in Pannekoek where this teaching is made. Applicants respectfully request that this passage be cited for their consideration.

Applicants respectfully request that rejection of claims 1, 5-6, 8, 10 and 17 under 35 U.S.C. § 102 be reconsidered and withdrawn.

Summary

Respectfully submitted,
D. Cines and A. A. Higazi

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(Date)

By: Ellen M. Klann

ELLEN M. KLANN, Ph.D.
Patent Agent
Registration No. 44,836
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-5368
Facsimile: (215) 963-5001
E-Mail: eklann@morganlewis.com
Agent for Applicants

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